REMARKS

Favorable reconsideration of the instant application is respectfully requested in view of the above amendments and the following remarks. The present Amendment is filed in response to the Office Action mailed March 9, 2005. By the present Amendment, claims 32, 34, 35, 38-41, 44-48, 64, and 65 are canceled, claims 43 and 67 are amended to remove reference to canceled claims, claim 66 is amended, and claim 68 is added to more specifically describe particular aspects of the claimed invention. Support for these amendments may be found throughout the specification and claims as originally filed, and, thus, these amendments do not constitute new matter. It should also be noted that the above amendments are made without prejudice to prosecution of any subject matter removed or modified by amendment in a related divisional, continuation or continuation-in-part application.

Telephone Interview

Applicants thank the Examiner for conducting a telephone interview on July 5, 2005, wherein the bases of the outstanding rejections and the cited prior art were discussed. Applicants thank the Examiner for his helpful comments regarding minor amendments to be made to further clarify the claimed subject matter. In this regard, Applicants note that claim 36 has been amended to replace the phrase "free vinorelbine" with "vinorelbine in solution," in accordance with the Examiner's suggestion. Support for this amendment is provided, *e.g.*, on page 6, lines 19-20, which indicates that the term "free" may be used interchangeably with "in solution."

In addition, claim 36 has been amended to recite the sphingomyelin/cholesterol ratio of 75/25 mol%/mol% sphingomyelin/cholesterol to about 30/50 mol%/mol%, instead of 35/50, which is a typographical error. Support for the presently claimed range is provided, *e.g.*, on page 8, line 25, of the instant specification.

Double Patenting Rejection

Claims 32, 34, 35, 39-41, 43 and 67 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over

claims 1, 2, 4, 5, and 17 of copending Application No. 09/896,811. The Examiner notes that while the conflicting claims are not identical, they are not patentably distinct from each other, because the claims in both applications are drawn to liposomal compositions comprising camptothecin, sphingomyelin, and cholesterol, and include generic claims deemed to include the specific limitations recited in the applications.

Without acquiescence to this basis of rejection, Applicants submit that claims 32, 34, 35, 39-41 are canceled by the present amendment, and claims 43 and 67 are amended to remove reference to canceled claim 32. Accordingly, the remaining claims do not recite a camptothecin. Applicants submit that the amendment thereby obviates this basis of rejection and respectfully requests that it be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 32, 34, and 35 stand rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Madden *et al.* (Proc. of ASCO, 1998). The Examiner asserts that it is implicit that topotecan is in at least 50% precipitated form in the liposomal formulations described by Madden *et al.*, given that topotecan is extremely insoluble in water, and the liposomes have an aqueous interior.

Applicants traverse this basis of rejection and submit that it is not implicit that the liposomal topotecan formulations described in Madden *et al.* have at least 50% precipitated topotecan. Contrary to the Examiner's assertion, Applicants submit that topotecan is a water-soluble derivative of camptothecin, as described on page 1, paragraph 5, of the instant specification. Accordingly, it would not be implicit that at least 50% of encapsulated topotecan would be precipitated in the liposomal topotecan formulations described by Madden *et al.*

However, Applicants note that without acquiescence to this basis of rejection, claims 32, 34, and 35 are canceled by the present amendment, thereby obviating this basis of rejection. Applicants, therefore, respectfully request that this basis of rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a) - Madden et al.

Claims 39-41, 43, and 67 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Madden *et al.* Specifically, the Examiner asserts that although Madden *et al.* does not provide details regarding drug:lipid ratios or sphingomyelin: cholesterol ratios, it would be obvious for one of skill in the art to manipulate these ratios to obtain the best possible results.

Applicants respectfully traverse this basis of rejection and submit that the claimed liposomal compositions are not obvious in light of Madden *et al.* Applicants note that for a reference to render a claimed invention obvious, it must teach or suggest each element of the claimed invention. In the instant case, Madden *et al.* does not teach the claimed drug:lipid or sphingomyelin:cholesterol ratios or associated advantages, and, therefore, does not teach each element of the claimed invention, as required to establish a *prima facie* case of obviousness.

Nonetheless, without acquiescence to this basis of rejection, claims 39-41 arecanceled, and claims 43 and 67 are amended, by the present amendment, thereby removing reference to topotecan and obviating this basis of rejection. Accordingly, Applicants respectfully request that this basis of rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a) - Kirpotin and Webb

Claims 32, 34-36, 38-41, and 64-67 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kirpotin (U.S. Patent No. 6,110,491), by itself or in combination with Webb (U.S. Patent 5,543,152). The Examiner asserts that Kirpotin discloses liposomal compositions comprising a precipitated active agent, and teaches that such active agents include antineoplastic agents, including vincristine, vinblastine, and vinorelbine. The Examiner further asserts that Kirpotin teaches that liposomes may comprise sphingomyelin or cholesterol, although Kirpotin's examples include only liposomes made from phosphatidlycholine and not sphingomyelin. In addition, the Examiner asserts that the use of liposomes comprising sphingomyelin would have been obvious in light of Webb, which teaches advantages of liposomes comprising sphingomyelin and cholesterol. The Examiner also asserts that the liposomal compositions described by Kirpotin fall within the claimed drug:lipid ratios,

although Kirpotin does not disclose the drug:lipid ratios or describe any specific ranges of ratios as being preferred in any of the passages cited by the Examiner.

Applicants respectfully traverse this basis of rejection and submit that the claimed subject matter is not obvious in light of Kirpotin, alone or in combination with Webb. As a first matter, Applicants note that claims 32, 34, 35, and 39-41 are canceled by the present amendment, without acquiescence to this basis of rejection. In addition, claim 67 is amended to remove reference to claim 32. Accordingly, the remaining claims are directed to liposomal compositions comprising vinorelbine, wherein the vinorelbine is present at specifically recited drug:lipid ratios that fall within the broadest claimed range of 0.1-0.5:1 (w/w).

Applicants respectfully submit that Kirpotin fails to render the presently claimed invention obvious, alone or in combination with Webb. The presently claimed invention is directed to specific liposomal vinorelbine compositions, wherein both the liposome components and the drug:lipid ratio are identified, as based upon the present inventors' discovery of specific liposomal vinorelbine formulations having superior properties. Specifically, liposomal vinorelbine formulations having the claimed features possess superior pharmacokinetic properties, including slower drug release. As shown in Figure 1, as the drug:lipid ratio is increased from 0.1:1 to 0.2:1 to 0.3:1, there is a corresponding increase in drug retention, which is. associated with drug precipitation in the liposomal interior. Furthermore, there is a corresponding reduction in the blood clearance half-life for vinorelbine. As is understood in the art and described in the instant specification, a slower release rate and slower blood clearance half-life is preferable and more efficacious, particularly in the treatment of tumors, including those typically treated with vinorelbine. Thus, the claimed liposomal vinorelbine formulations, having a drug:lipid ratio of 0.1-0.5:1 (w/w), such that at least 50% of the total vinorelbine is precipitated, are identified according to the instant specification, possess previously unrecognized advantages and, thus, are not obvious in light of the cited art.

Applicants submit that while Kirpotin may broadly reference liposomal compositions of the same drug, Kirpotin absolutely fails to teach a liposomal composition comprising the specifically claimed liposome components (*i.e.*, sphingomyelin and cholesterol in the range of about 75/25 mol%/mol% to about 30/50 mol%/mol%) and the claimed

vinorelbine:lipid ratios (*i.e.*, 0.1 to 0.5 (w/w)), which combination is identified, according to the present invention, as possessing superior pharmacokinetic properties. Applicants further submit that the deficiencies of Kirpotin are not rectified by Webb, which also fails to teach or suggest these features or the combination of features present in the specifically claimed liposomal formulations.

As described in the instant specification, not all lipid formulations are equal for drug delivery purposes, and the optimal drug:lipid ratio varies for different drugs. Thus, extensive research continues in an effort to identify formulations that demonstrate preferred characteristics for drug loading and storage, drug administration, pharmacokinetics, biodistribution, leakage rates, tumor accumulation, toxicity, and other features (paragraph 6). Accordingly, the identification and selection of a preferred liposomal drug formulation with advantageous properties requires considerable effort and experimentation, and is not obvious over a reference that fails to identify the specific features of the preferred liposomal drug formulation.

In addition, the skilled artisan would appreciate that the specific liposome components (*e.g.*, lipids), the particular drug, and the particular drug:lipid ratio are all variable features of liposomal formulations, each of which contributes to the pharmacokinetic properties of a liposomal drug formulation. Furthermore, these properties are not independent of each other, as the characteristics of a particular drug (*e.g.*, solubility, half-life, and size) will contribute to determining the best combination of these features. Thus, the identification of a specific combination of lipid components and drug:lipid ratio for a particular drug, which provides superior pharmacokinetic properties for that drug, requires more than merely routine experimentation. Accordingly, Applicants submit that the presently claimed invention cannot be found obvious over Kirpotin, alone or in combination with Webb, which also fails to teach or suggest liposomal formulations having the claimed combination of features. Applicants respectfully request that this basis of rejection be withdrawn, in light of the above amendments and these comments.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. However, should any remaining issues exist, the Examiner is urged to contact Applicants' undersigned representative at (206) 622-4900.

Respectfully submitted,

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